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EXAMINER
SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/979,545	HWANG ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant is advised that the examiner reviewing this application has changed. Please address future correspondence to Juliet Switzer, Art Unit 1634.

This action is written in response to applicant's correspondence submitted 5/27/03. Claims 1-18 have been canceled and claims 19-25 have been added. Claims 19-25 are pending and examined herein. New grounds of rejection are set forth to address the amended claims. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Restriction Requirement

1. Applicant's election with traverse of Group I in the paper filed 5/27/03 is acknowledged. The traversal is on the ground(s) that it would not be an unreasonable burden on the examiner to examine both groups together as the kit of claim 18 is "for substantially exclusively using the method claims of group I (p. 7 of response)." This is not found persuasive because as noted in the previous office action, the kits of claim 17 could be used in other methods besides the methods of claims 18-25. Further, the search of the kits would require a separate word search using different terms and identifiers than the method of group II, and a search of different classifications, as is exemplified by the fact that the kits are separately classified from the methods. The requirement is still deemed proper and is therefore made FINAL.

Specification

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Regarding claims 19-25, the claims are drawn to a method of identifying a DNA mutation, however the method steps recite a series of steps which result in the detecting and comparing of hybridization between a control group and a test group of microwells, and determining whether the sample hybridizes to the first sequence or the second sequence based on the degree of hybridization in the microwells. The method steps do not set forth how these steps accomplish the recited objective of identifying a DNA mutation, as they never recite a mutation, or probes for detecting a mutaiton, etc. The claims should be amended either to add the method steps necessary to accomplish the identification of a DNA mutant or to clarify how detection of hybridization accomplishes the recited objective of the method.

b. Claims 19-25 are indefinite over the recitation "a sample nucleotide" because it is not clear if applicant means a single nucleotide or a nucleic acid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 19, 22, 23, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu *et al.* (Hum. Immun. 1993, 37, p. 141, abstract #270) in view of Zammatteo *et al.* (Analytical Biochemistry 236:85-94, 1996).

Wu *et al.* teaches a method for identifying a mutation in a nucleotide sequence, the method comprising:

providing a plurality of polystyrene microwells (Wu *et al.* utilize "microtiter plates" which inherently have a plurality of microwells);

partitioning the plurality of aminated polystyrene microwells into a control group and at least one test group (Sequence specific probes to different alleles of HLA DR DNA are immobilized in the wells. Any one of these alleles can be designated as "control" and "test") ;

covalently immobilizing probes comprising a 5' phosphate group and a nucleotide sequence to the polystyrene microwells by the 5' phosphate group, wherein probes encoding a

nucleotide sequence complementary to a first sequence are immobilized in microwells of the control group and probes encoding a second nucleotide sequence are immobilized in microwells of the at least one test group (Sequence specific probes to different alleles of HLA DR DNA are immobilized in the wells via their 5'-end, which inherently has a phosphate group. Any one of these alleles can be designated as "control" and "test);

providing a sample nucleotide for testing to the plurality of microwells, wherein the sample nucleotide is biotinylated ("Biotynlated short nucleic acid fragments are added to each well");

hybridizing the sample nucleotide to the plurality of microwells with the immobilized probes under hybridization conditions (The fragments are "hybridized at a designated temperature for 30 minutes.");

detecting the degree of hybridization in the microwells of the control group and the microwells of the at least one test group (Hybridization is detected using streptavidin-alkaline phosphatase conjugate and enzymatic substrate);

comparing the degree of hybridization in the microwells of the control group to the degree of hybridization in the at least one test group (Color reaction in the wells is determined using an conventional ELISA reader); and

determining whether the sample nucleotide hybridizes to the first sequence of the second sequence based on the degree of hybridization in the microwells (Allele is assigned based on hybridization results).

95 ~~; 22, 23, and 25~~

With regard to claim 22, Wu *et al.* detect the degree of hybridization comprises adding a streptavidin-linked degradation enzyme to the microwells, whereby the degradation enzyme is bound to the biotin moiety of the sample nucleotide hybridized to the probes (Wu *et al.* state, "Streptavidin-alkaline phosphatase conjugate (SA-AP) solution is then added and incubated..."); and

adding to the microwells a compound degradable by the degradation enzyme (Wu *et al.* state "Enzymatic substrate is added"); and determining the extent of compound degradation (Color reaction in the wells is determined using an conventional ELISA reader).

With regard to claim 23, the degradation enzyme is alkaline phosphatase (Wu *et al.* state, "Streptavidin-alkaline phosphatase conjugate (SA-AP) solution is then added and incubated...").

With regard to claim 25, the determining the extent of compound degradation is accomplished by determining the optical density of the microwell after the compound degradable by the degradation enzyme is provided to the degradation enzyme (Wu *et al.* complete this step with an ELISA reader to detect the colorimetric reaction).

Wu *et al.* state that the oligonucleotide probes are linked to microtiter plates via their 5' end "using proprietary chemistry." Thus, they do not disclose providing a plurality of aminated polystyrene microwells or immobilizing the probes to the aminated polystyrene microwells.

Zammatteo *et al.* teach that a routine method for attaching DNA probes for hybridization assays is a by a condensation of amines (on the polystyrene wells) with the 5'-end phosphate of DNA, and that an advantage of this reaction is that a higher proportion of end attachment is obtained, compared to binding of aminated DNA onto carboxylated substrates. Zammatteo *et al.* teach that the surface of polystyrene wells, can be modified to introduce specific functions, and

that since amine groups can be readily used for covalent linking of biomolecules. Thus, Zamatteo *et al.* teach providing a plurality of aminated polystyrene microwells.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Wu *et al.* so as to have included a step of providing the aminated polystyrene microwells taught by Zammatteo *et al.* for attachment of the probes taught by Wu *et al.* On would have been motivated to combine the methods in order to use a method for attaching probes to microwells that results in a high proportion of attachment, in order to practice the methods taught by Wu *et al.* for the detection of particular alleles in samples.

5. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable Wu *et al.* (Hum. Immun. 1993, 37, p. 141, abstract #270) in view of Zammatteo *et al.* (Analytical Biochemistry 236:85-94, 1996), as applied to claims 19, 22, 23, and 25 above, in further view of Saiki *et al.* (PNAS USA, Vol. 86, p. 6230-6234, August 1989).

The teachings of Wu *et al.* in view of Zammatteo *et al.* as applied to claims 19, 22, 23, and 25 are applied to this rejection as they were previously applied.

Wu *et al.* in view of Zammatteo *et al.* do not teach the length of the nucleotide probes used in their methods, specifically they do not teach that the probes are more than 10 nucleotides.

However, the use of probes of more than 10 nucleotides was routine in the art at the time the invention was made, as is exemplified by the probes utilized by Saiki *et al.* (see Table 1, p. 6232, for example). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized probes comprising more than ten nucleotides in the methods of Wu *et al.* in view of Zammatteo *et al.* One would have been

motivated to provide such probes so that they would have been of sufficient length to specifically hybridize to target sequences.

6. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable Wu *et al.* (Hum. Immun. 1993, 37, p. 141, abstract #270) in view of Zammatteo *et al.* (Analytical Biochemistry 236:85-94, 1996), as applied to claims 19, 22, 23, and 25 above, in further view of Felder and Kris, USPN 6232066, filed July 2, 1998, issued May 15, 2001.

The teachings of Wu *et al.* in view of Zammatteo *et al.* as applied to claims 19, 22, 23, and 25 are applied to this rejection as they were previously applied.

Wu *et al.* in view of Zammatteo *et al.* do not specifically provide the details of their hybridization solution, and in particular they do not teach a hybridization solution containing 20x SSPE, 0.0167% Triton X-100™, and 10 mg/ml salmon sperm DNA.

The use of hybridization buffers containing SSPE, Triton X-100™, and salmon sperm DNA were well known to those of ordinary skill in the art at the time the application was filed (see, for example Felder, column 30, line 39, and column 12, lines 13-15). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki to include the buffer of Felder. One of ordinary skill would have been motivated to include the buffer of Felder due to the presence of salmon sperm DNA, an agent known to block non-specific binding of DNA (Felder, column 12, lines 13-15).

Felder does not teach the specific concentrations of SSPE, Triton X-100™, or salmon sperm used in the instant application. However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to optimize the method of Saiki and the buffer of Felder in order to minimize non-specific binding of the single-stranded probe.

7. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over in further view of Zreiqat.

The teachings of Wu *et al.* in view of Zammatteo *et al.* as applied to claims 19, 22, 23, and 25 are applied to this rejection as they were previously applied.

Wu *et al.* in view of Zammatteo *et al.* do not teach that the compound degradable by the degradation enzyme is pNPP (p-nitrophenyl phosphate).

However, the use pNPP as a substrate for alkaline phosphatase was well known to those of ordinary skill in the art at the time the application was filed. Zreiqat, for example, teaches a the use of alkaline phosphatase and pNPP in an in situ hybridization technique for the detection of mRNA. (Zreiqat, page 107, abstract). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Saiki to incorporate a alkaline phosphatase and pNPP in order to allow a rapid and quantitative measure of the amount of enzyme present in the microwell.

Response to Remarks

Applicant's remarks address the previous rejections, which have been withdrawn. New rejections are set forth which address the limitations of the newly added claims. Thus the remarks are moot in light of the new grounds of rejection.

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

August 9, 2003

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
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